



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

|                              |   |                           |
|------------------------------|---|---------------------------|
| In re Patent Application of: | ) | Art Unit: 1654            |
|                              | ) |                           |
| SZARDENINGS, et al.          | ) | Examiner: CHISM, B.       |
|                              | ) |                           |
| Serial No: 09/674,733        | ) | Washington, D.C.          |
|                              | ) |                           |
| Filed: May 2, 2001           | ) |                           |
|                              | ) |                           |
| For: MELANOCORTIN 1 RECEPTOR | ) | Docket No.: SZARDENINGS=1 |
| SELECTIVE COMPOUNDS          | ) |                           |
|                              | ) | Confirmation No.: 3759    |

**DECLARATION OF THOMAS JONASSEN**

U.S. Patent and Trademark Office  
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I hereby declare:

1. I am one of the inventors of the above-identified patent application.
2. I am a M.D. and Associate Professor in Cardiovascular and Renal Pharmacology at the University of Copenhagen. My curriculum vitae is attached.
3. I am an employee of ACTION PHARMA A/S and I presently hold the position of Chief Scientific Officer.
4. Attached hereto as exhibit 1 is a two-page document entitled "inhibition of LPS induced TNF $\alpha$  production in rats *in vivo*", and including a Figure 1. This exhibit is hereby incorporated by reference into this declaration. It describes experiments carried out by myself and/or under my supervision.
5. The results show that compounds MS05 and MS09 inhibit TNF $\alpha$  production in rats *in vivo*, consistent with claim 21.

$\alpha$ -MSH has been shown to have marked anti-inflammatory effects *in vitro* and *in vivo* that includes melanocortin type 1 receptor (MC1) mediated stimulation of the release of the cytokine synthesis inhibitor IL-10 from monocytes (J Immunol 156; 2517-21, 1996) and downregulation of the synthesis and release of the proinflammatory cytokines IL-1; IL-6 and TNF- $\alpha$  (Immunol Today 18; 140-45, 1997) as well as the production of NOS mediated NO by macrophages (J Leukoc Biol 59; 248-53, 1996). Therefore a compound that binds

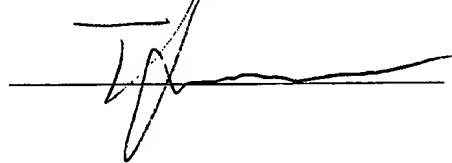
to and activates MC1 receptors with the same or higher affinity and efficacy as  $\alpha$ MSH and has proven effective in order to reduce LPS induced TNF $\alpha$  production in a similar or even more pronounced way than  $\alpha$ MSH, will also have the ability to inhibit LPS induced IL-1 and IL-6 production. Both MS05 and MS09 fulfils these criteria's since both peptides have binding affinities for the MC1 receptor that are comparable with  $\alpha$ MSH and both peptides have the same maximal efficacy on MC1 receptor activation as  $\alpha$ MSH (Peptides 21, 239-43, 2000).

It is well-described that inducible nitric oxide synthase (iNOS) is transcriptional induced by bacterial constituents and inflammatory mediators, including TNF- $\alpha$  and IL-1. It is therefore most certain that a peptide as MS05 or MS09 that have the ability to inhibit LPS induced TNF- $\alpha$  liberation will inhibit NOS activity and thereby NO accumulation.

*I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.*

Date: 25/5-05

By: Thomas Engelbrecht Nordkild Jonassen

A handwritten signature in black ink, appearing to be 'T. Engelbrecht', written over a horizontal line.

## CURRICULUM VITAE

|                                    |   |
|------------------------------------|---|
| <b>Name</b>                        | <b>Thomas Engelbrecht Nordkild Jonassen, MD</b>   |
| <b>Date of Birth</b>               | 17. September. 1963, Gentofte, Denmark.   |
| <b>Office Address</b>              | Department of Pharmacology<br>Laboratory of Cardiovascular and Renal Pharmacology<br>The Panum Institute, University of Copenhagen<br>tlph: +45 35 32 76 16; FAX +45 35 32 76 10.<br>E-mail: fitj@farmakol.ku.dk  |
| <b>Home address</b>                | Pile Alle 20, 2830 Holte, Denmark   |
| <b>Education</b>                   | MD degree 1995, University of Copenhagen<br>Clinical training 1995-97 at Kalundborg Sygehus and Herlev University Hospital.   |
| <b>Position</b>                    | 1993. Pregraduate Research Fellow at the Department of Pharmacology, University of Copenhagen.<br>1995-1996. Recidency at Kalundborg Sygehus<br>1996-1998. Research Fellow, Department of Pharmacology, University of Copenhagen.<br>1998-2000. Assistant Professor, Department of Pharmacology, University of Copenhagen<br>2000-present. Associate Professor, Department of Pharmacology, University of Copenhagen<br>2004-present. Chief Scientific Officer, Action Pharma (part time) |
| <b>Research Interests</b>          | Research focus on integrative pharmacology/pathophysiology with special focus on renal dysfunction in congestive heart failure and liver cirrhosis. Additional focus on pulmonary microvascular permeability and alveolar fluid resolution in Congestive heart failure.   |
| <b>Supervision</b>                 | Supervisor for 4 Ph.D. students that have completed their thesis (all at the University of Copenhagen). Currently supervisor for 4 Ph.D. students (at the University of Copenhagen).  |
| <b>Publications</b>                | 26 original papers (all in international journals) and 3 patents.   |
| <b>International Collaborators</b> | Professor Daniel Kapusta, PhD, New Orleans, LS, USA.<br>Professor Peter Deen, PhD, Nijmegen, The Netherlands<br>Professor Gerald DiBona, MD, Iowa City, Iowa, USA   |

**Thomas Engelbrecht Nordkild Jonassen, MD**

Ten selected publications

1. Jonassen, T.E.N., N. Marcussen, K. Haugan, H. Skyum, S. Christensen, F. Andreasen, and J.S. Petersen: Functional and structural changes in the thick ascending limb of Henle's loop in rats with liver cirrhosis. *Am. J. Physiol. Regulatory and Integrative Physiol.* 273: R568-R577. 1997.
2. Jonassen, T.E.N., S. Nielsen, S. Christensen, and J.S. Petersen: Decreased vasopressin-mediated renal water reabsorption in rats with compensated liver cirrhosis. *Am. J. Physiol. Renal Physiol.* 275: F216-F225, 1998.
3. Jonassen, T.E.N., S. Christensen, N. Marcussen, A.-M. Sørensen, A. Flyvbjerg, F. Andreasen, and J.S. Petersen. Effects of chronic octreotide treatment on renal changes during compensated liver cirrhosis in rats. *Hepatology* 29:1387-95, 1999.
4. Jonassen, T.E.N., D. Promeneur, S. Christensen, J.S. Petersen, and S. Nielsen. Decreased vasopressin-mediated renal water reabsorption in rats with chronic aldosterone-receptor blockade. *Am. J. Physiol. Renal Physiol.* 278: F246-F256, 2000.
5. Jonassen T.E.N., S. Christensen, Tae-Hwan Kwon, S. Langhoff, N. Salling, and S. Nielsen: Renal water handling in rats with decompensated liver cirrhosis. *Am. J. Physiol.* 279: F1101-F1109, 2000.
6. Staahltoft D., S. Nielsen, N.R. Janjua, S. Christensen, N. Marcussen, O. Skøtt and T.E.N. Jonassen: Chronic losartan treatment normalizes renal water handling in rats with congestive heart failure. *Am. J. Physiol. Renal Physiol.* 282: F307-F315, 2002
7. Jonassen T.E.N., L. Brønd, M. Torp, M. Græbe, S Nielsen, O Skøtt, N. Marcussen and S Christensen: Effects of renal denervation on thick ascending Na reabsorption in rats with liver cirrhosis. *Am. J. Physiol. Renal Physiol.* 284: F555-63, 2003
8. Græbe M., L Brønd, S Nielsen, S Christensen, NV Olsen and T.E.N. Jonassen: Chronic Nitric Oxide Synthase Inhibition Exacerbate Renal Dysfunction in Cirrhotic Rats. *Am J Physiol Renal Physiol.* 286:F288-97, 2004
9. Hadrup N, J.S. Petersen, J. Praetorius, E. Meier, M. Græbe; L. Brønd; D. Staahltoft; S. Nielsen, S. Christensen and T.E.N. Jonassen. Opioid receptor-like 1 stimulation in the collecting duct induces aquaresis through vasopressin-independent aquaporin-2 downregulation. *Am J Physiol Renal Physiol.* 287:F160-8, 2004
10. Brønd L., N. Salling, S. Christensen, S. Nielsen, M. Græbe and T.E.N. Jonassen: Uncoupling of vasopressin signaling in collecting ducts from rats with CBL induced liver cirrhosis. *Am J Physiol Renal Physiol.* 287:F806-15, 2004